REMARKS

Claims 1-30 and 32-36 are pending in the application. Claim 1-21, 30 and 31-36 have previously been withdrawn from consideration as directed to a non-elected invention and are canceled herein. Claims 22-29 are presently under examination. Claims 25 and 26 have been amended to spell out claim terms. No new matter has been introduced by the amendments to claim 26 and entry is respectfully requested.

Regarding the Claim Objections

The Examiner has asserted that "test progeny are produced" is grammatically incorrect. The Examiner is respectfully submitted to be mistaken in his assertion. Progeny is a noun that can be either singular or plural depending on the context (other examples of such nouns include, for example, "aircraft" and "species"). *See, for example*, Scientific Style and Format: the CBE Manual for Authors, Editors, and Publishers, Sixth Edition, Cambridge University Press.

Claim 24 has been amended to spell out the names of the recited genes. Applicants respectfully request removal of the claim objections.

Regarding 35 U.S.C. § 112, First Paragraph

Written Description

Applicants traverse the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Base claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene and a second parent strain containing a genetic variation, whereby test progeny are produced, where, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of the first parent strain, the second parent strain and the test progeny; and assaying the test progeny for the altered phenotype, wherein a modification of the altered phenotype producing a phenotype with more

similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

The Examiner asserts that, as of the effective filing date, APP, presenilin 1 and presenilin 2 were known to associate with Alzheimer's disease and cites to support by Duff et al., WO 98/17782 and Mucke et al., U.S. Patent No. 6,455,757. The Examiner further wonders which mutation features for genes such as har38, α-adaptin, garnet, mastermind or big brain would associate these genes with Alzheimers disease. It is respectfully submitted that third party references are irrelevant to whether the specification provides written description for the claimed methods. The specification discloses numerous Alzheimer's disease genes with which one skilled in the art can practice the invention and further provides additional exemplary Alzheimer's disease genes, including genes disclosed in the specification itself as interacting (directly or indirectly) with *Appl*. Additional Alzheimer's disease genes that are disclosed in the specification, for example at page 14, as useful for practicing the methods of the invention include, for example, *Notch* (N), *Suppressor of Hairless* (Su(H)), *Delta* (Dl), *mastermind* (mam), *big brain* (bib), *halothane resistant* (har38), *cAMP-responsive element-binding protein A* (CrebA), *cAMP-responsive element-binding protein B* (CrebB, activator), *cAMP-responsive element-binding protein B* (CrebB, inhibitor), *α-adaptin*, *garnet* (δ-adaptin), and *shibire* (shi)(dynamin). Furthermore, with regard to the Examiner's query about how other genes (har 38, α-adaptin *etc.*) are associated with Alzheimer's disease, the specification teaches that an Alzheimer's disease gene can be a gene that is differentially expressed at the mRNA or protein level in $Appl^{d}$ flies as compared to $Appl^{+}$ flies and discloses several dozen specific examples of such Alzheimer's disease genes in Tables 4-6. One skilled in the art understand would have appreciated that Applicants were in possession of parental strains other than the Drosophila $Appl^{D}$, in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding lack of written description for transgenic methods, Applicants point out that, as taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the

invention (page 17, lines 1-10). In this regard, the specification further describes that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

The Examiner alleges that the skilled person cannot envision altered phenotypes that may be observed in the progeny. Applicants submit that the specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

Further with regard to observable phenotypes, the specification teaches that viability is particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls. With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the

test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. §112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Enablement

The specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

The specification teaches that viability is an observable phenotype particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of $Appl^{d}$ and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying $Appl^{d}$ and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls.

With regard to a behavioral phenotype, Example III, shows that $Appl^{d}$ Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant

change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding non-enablement of transgenic methods, Applicants point out that enablement of every single embodiment within the scope of the claims is not a prerequisite for the enablement of the claimed methods. As taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further teaches that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

At the time of filing, those skilled in the art had knowledge that human disease gene homologs had been identified in a variety of genetic systems and, given the broad teachings and guidance for the use and applicability of the claimed methods with regard to species other than Drosophila, would have appreciated Applicants possession of the full scope of the claimed invention. In this regard the specification teaches, for example, at page 17, lines 14-29, homologs of human disease genes in a variety of other genetic systems including zebrafish, nematodes and yeast.

For the various embodiments, the specification provides guidance with regard to practicing the invention in strains corresponding to a variety of genetic systems, for example, at

page 39, lines 19-26, which discusses particular modes of administering an agent to mice, nematodes zebrafish and yeast.

With regard to phenotypes useful for practicing the invention, the specification teaches that useful phenotypes include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast. These teachings would have conveyed to the skilled person, at the time of filing, that Applicants, while exemplifying the claimed methods using Drosophila, were in possession of the full scope of their claimed invention, which includes practice of the methods of identifying a therapeutic agent for treating Alzheimer's disease, in strains other than Drosophila and by utilizing transmission genetics.

Regarding 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 22-29 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The Court of Appeals for the Federal Circuit has held and repeatedly affirmed that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, e.g., In *re Marosi*, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); and *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999) (district court failed to consider the knowledge of one skilled in the art when interpreting the patent disclosure).

The Examiner professes to be unclear as to what is encompassed by the phrase assaying the test progeny for the altered phenotype" in step (c) of claim 22. The Examiner queries which test progeny and/or which altered phenotype Applicants refer to and wonders whether it is he test

progeny with an altered phenotype recite in step (a). The relevance of step (b) in administering an agent to the first parent strain or the second parent strain in context of step (c) for assaying the test progeny that "already has altered phenotype as recited in step (a)" is questioned. Furthermore, the Examiner professes not to understand the phrase "producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type."

Applicants respectfully submit that the claim is clear, concise and self-explanatory. Antecedent basis is used correctly and the claim was drafted carefully. Several Examiner's have been assigned to this application and the clarity of the claim has not been an issue. Furthermore, Applicants respectfully take issue with the Examiner's admission that he basically does not understand a single step of the claim in light of the numerous "modified" and new rejections that were raised.

Applicants submit that, when viewed in light of the specification of which they are part, claims 22-29 are sufficiently clear and definite to the skilled person to comply with the second paragraph of section 112 of the Code.

Regarding 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 22-23, 25 and 28 under 35 U.S.C. § 102(e) as allegedly being anticipated by Mucke et al., U.S. Patent No. 6,455,757. Applicants further respectfully traverse the separate rejection of claims 22-23, 25 and 28 under 35 U.S.C. § 102(b) as allegedly being anticipated by Duff et al., WO 98/17782.

Claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene and a second parent strain containing a genetic variation, whereby test progeny are produced, wherein, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of said first parent strain, said second parent strain and said test progeny; and assaying the test progeny for the altered phenotype, wherein a modification of the altered phenotype producing a phenotype with more

similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

When lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, (Fed. Cir. 1998) (quoting *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544-45, 24 U.S.P.Q.2d 1133, 1136 (Fed. Cir. 1992)). To establish a *prima facie* case of anticipation, the Office must show that the single reference cited as anticipatory art describes all the elements of the claimed invention.

The Examiner has not pointed out where Mucke et al. teaches that an agent is administered to the test progeny and the test progeny subsequently assayed for whether the administration of the agent resulted in a modification of an altered phenotype producing a phenotype that is more like the wild type than the phenotype than the altered phenotype. Accordingly, the Examiner has not established a prima facie case required and removal of the rejection of claims 22-23, 25 and 28 under 35 U.S.C. § 102(e) as allegedly being anticipated by Mucke et al., U.S. Patent No. 6,455,757, is respectfully requested.

The Examiner has not pointed out where Duff et al. teaches that administration of the agent resulted in a modification of an altered phenotype producing a phenotype that is more like the wild type than the phenotype than the altered phenotype. Accordingly, the Examiner has not established a prima facie case required and removal of the rejection of claims 22-23, 25 and 28 under 35 U.S.C. § 102(e) as allegedly being anticipated by Duff et al., WO 98/17782, is respectfully requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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